PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 211/22, 453/02 — A1

(11) International Publication Number: **WO 96/19452**

(43) International Publication Date: 27 June 1996 (27.06.96)

(21) International Application Number: PCT/EP95/04975

(22) International Filing Date: 15 December 1995 (15.12.95)

(30) Priority Data:
1455/94 21 December 1994 (21.12.94) DK

(71) Applicant *(for all designated States except US)*: NEUROSEARCH A/S [DK/DK]; Smedeland 26B, DK-2600 Glostrup (DK).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: PETERS, Dan [SE/SE]; Almbacksgatan 11B, S-211 54 Malmö (SE). AXELSSON, Oskar [SE/SE]; Stora Kvarngatan 5-604, S-211 27 Malmö (SE).

(74) Agent: GRÜNECKER, KINKELDEY, STOCKMAIR & SCHWANHÄUSSER; Maximilianstrasse 58, D-80538 München (DE).

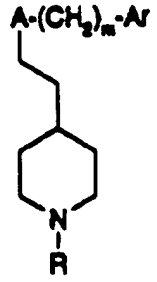
(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: A PROCESS FOR THE PREPARATION OF SUBSTITUTED 4-ETHYL-PIPERIDINES AND AN INTERMEDIATE FOR THE PREPARATION OF SAME

(57) Abstract

The invention relates to a process for the preparation of substituted 4-ethyl-piperidines having formula (I), or a salt thereof, wherein R is $(aryl)_p$alkyl, $(aryl)_p$alkenyl or $(aryl)_p$alkynyl, wherein the aryl groups may be substituted; cycloalkyl; or cycloalkylalkyl; p is 0, 1 or 2; m is 0, 1, 2, 3, 4, 5 or 6; A is O, S or NR^1, wherein R^1 is hydrogen, alkyl or phenylalkyl; an Ar is aryl or heteroaryl, each of which may be substituted; which comprises the step of reacting a quinuclidinium salt of formula (a), wherein R is as defined above and Y is a counter ion, with a compound of the formula: $HA-(CH_2)_m-Ar$ or a reactive derivative thereof, and thereafter optionally forming a salt thereof.



(I)

(a)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SI	Slovenia
SK	Slovakia
SN	Senegal
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

A PROCESS FOR THE PREPARATION OF SUBSTITUTED 4-ETHYL-PIPERIDINES AND AN INTERMEDIATE FOR THE PREPARATION OF SAME.

Field of Invention

The present invention relates to a novel process for the preparation of substituted 4-ethyl-piperidines and intermediates for the preparation of same. The substituted 4-ethyl-piperidines prepared according to the invention are useful in therapy as calcium channel blocking agents.

Background of Invention and Prior art

The substituted 4-ethyl-piperidines prepared according to the invention and their activity as calcium channel blocking agents are disclosed in WO-A1-92/02502, WO-A1-93/15052, and Neuropharmacology, Vol. 32, No. 11, p. 1249-1257 (1993).
These publications describes several methods for the preparation of the compounds, using piperidines or pyridines as starting materials.
It has now been found that substituted 4-ethyl-piperidines can be prepared by a very convenient, high yielding, one pot, two step synthesis, from readily available starting materials.

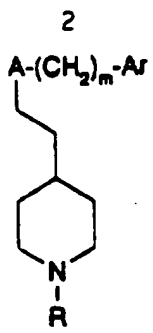
Objects of the Invention

It is the object of the present invention to provide a novel method for the preparation of substituted 4-ethyl-piperidines, which is convenient and high yielding, using readily available starting materials. Furthermore, it is an object of the present invention to provide novel intermediates useful for the preparation of substituted 4-ethyl-piperidines.

Summary of the Invention

In detail the invention, then, comprises inter alia the following:

A process for the preparation of substituted 4-ethyl-piperidines having the formula



or a salt thereof

wherein

R is $(aryl)_p$alkyl, $(aryl)_p$alkenyl or $(aryl)_p$alkynyl, wherein the aryl groups may be substituted; cycloalkyl; or cycloalkylalkyl;

p is 0, 1 or 2;

m is 0, 1, 2, 3, 4, 5 or 6;

A is O, S or NR^1, wherein R^1 is hydrogen, alkyl or phenylalkyl;

and Ar is aryl or heteroaryl, each of which may be substituted; which comprises the step of reacting a quinuclidinium salt of formula

wherein R is as defined above and Y is a counter ion, with a compound of the formula $HA-(CH_2)_m-Ar$ or a reactive derivative thereof, and thereafter optionally forming a salt thereof;

a process as above, wherein A is O;

a process as above, wherein m is 0 and Ar is 3, 4-dichlorophenyl;

a process as above, wherein R is pentyl;

a process as above, wherein the reaction takes place in the presence of a base;

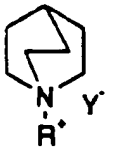
a process as above, wherein the base is an inorganic base;

a process as above, wherein the base is Cs_2CO_3;

a compound of the formula

wherein R and Y is as defined above; provided that when R is alkyl, the alkyl group contains at least three carbon atoms, and Y is not bromide; and

the use of a compound of the formula



wherein R and Y are as defined above, as an intermediate in the preparation of substituted 4-ethyl-piperidines.

To the above formulas the following applies:

Alkyl means a straight or branched chain of from one to eight carbon atoms, including but not limited to, methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, and heptyl.

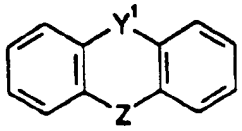
Alkenyl and alkynyl means straight or branched chains of from two to eight carbon atoms, with respectively, at least one double or triple bond, and including but not limited to ethenyl, 1,2- or 2,3 propenyl, 1,2- or 3,4-butenyl, ethynyl, 2,3-propynyl, 2,3- or 3,4-butynyl.

Cycloalkyl means cyclic alkyl of from three to eight carbon atoms, including but not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Cycloalkylalkyl is cycloalkyl and alkyl as above.

It is to be understood that the $(aryl)_p$alkyl, $(aryl)_p$alkenyl and $(aryl)_p$alkynyl and cycloalkylalkyl groups R, are linked to the piperidine nitrogen atom via the alkyl, alkenyl and alkynyl moieties respectively.

Suitable aryl groups include, for example, unsaturated, partially saturated or saturated monocyclic, bicyclic or tricyclic ring systems of up to fifteen carbon atoms, such as, for example, phenyl, naphthyl, tetrahydronaphthyl, fluorene, flurenone, dibenzosuberene, and dibenzosuberenone.

Suitable heteroaryl groups include, for example, unsaturated, partially saturated, or saturated monocyclic, bicyclic or tricyclic ring systems of up to fifteen carbon atoms containing at least one heteroatom, such as pyridyl, thienyl, imidazolyl, quinolinyl, tetrahydroquinolinyl, benzofuranyl. A tricyclyclic ring system most preferably has the structure:



wherein Y^1 represents $-X(CH_2)_r-$, X is O, S, or NR' (where R' is hydrogen or C_{1-4}alkyl), Z is $-(CH_2)_q-$ or -CH=CH-, q is 0,1 or 2 and r is 0 or 1 or is a corresponding dehydro ring system. Examples of tricyclic heteroaryl groups include dibenzofuranyl, dibenzothienyl, carbazole, N-methylcarbazole, acridine and dibenzooxepine. The heteroaryl ring can be linked to the remainder of formula via any suitable ring atom.

Suitable substituents on the aryl and heteroaryl rings includes, for example, 1-3 substituents selected from halogen, nitro, CN, CF_3, OCF_3, alkyl, alkoxy, alkylthio, NH_2, NHalkyl, $N(alkyl)_2$, C_{1-2}alkylenedioxy, and optionally substituted phenyl, phenoxy, benzoyl, phenylalkyl (e.g. benzyl), or phenylalkoxy (e.g. benzyloxy).

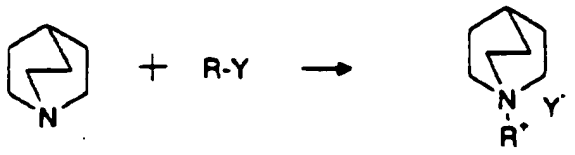
Suitable substituents on said optionally substituted phenyl, phenoxy, benzoyl, phenylalkyl and phenylalkoxy include for example alkyl, alkoxy, halogen, CF_3 and nitro.

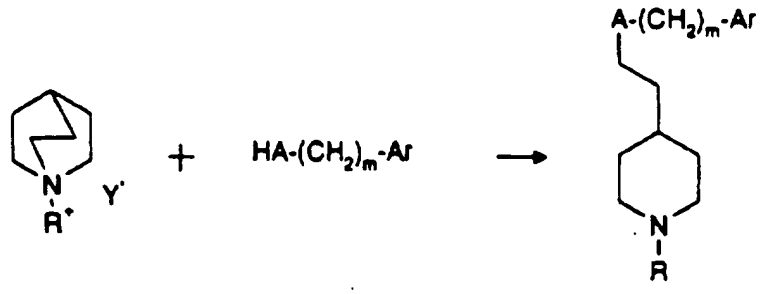
Examples of salts include pharmaceutically acceptable inorganic and organic acid addition salts such as the hydrochloride, hydrobromide, phosphate, nitrate, perchlorate, sulphate, citrate, lactate, tartrate, maleate, fumarate, mandelate, benzoate, ascorbate, cinnamate, benzenesulfonate, methanesulfonate, stearate, succinate, glutamate, glycollate, toluene-p-sulphonate, formate, malonate, naphthalene-2-sulphonate, salicylate and the acetate. Such salts are formed by procedures well known in the art.

Other acids, such as oxalic acid, may also be useful in the preparation of salts according to the invention.

The Invention

As already stated the invention provides a convenient, high yielding process for the preparation of substituted 4-ethyl-piperidines, using readily available starting materials. The following scheme illustrates the novel process of the invention, which is normally carried out as a one-pot reaction:





The quarternization of the quinuclidine ring may be carried out in conventional manner, without the use of solvent, or in an organic solvent, for example an alcohol, such as methanol, ethanol, isopropanol and phenol, an ether such as diisopropylether, tetrahydrofuran or dioxan, an amide such as dimethylformamide, or in a halogenated-,

aromatic- or aliphatic hydrocarbon such as chlorof rm, dichlormethan, benzene, toluen , xylene and hexane. Preferably the reaction is carried out without the use of solvent.

The leaving group Y may be a halide, such as bromide, chloride or iodide or a sulfonyloxy group such as methylsulphonyloxy, benzenesulphonyloxy, or p-toluenesulphonyloxy

Temperatures between 20°C and 200°C is appropriate for the reaction.

The ring opening reaction may be carried out without the use of solvent or in an inert solvent with high boiling point. Preferably the reaction is carried out without the use of solvent.

Preferably the ring opening reaction is carried out in the presence of an organic or inorganic base, for example hydroxides, such as NaOH, KOH, CsOH,or RbOH or carbonates, such as Na_2CO_3, K_2CO_3, Cs_2CO_3, Rb_2CO_3, $NaHCO_3$, $KHCO_3$, and $CsHCO_3$. Preferably the reaction takes place in the presence of Cs_2CO_3.

Temperatures between 100°C and 250°C, preferably between 150°C and 200°C, are appropriate for the reaction. Suitably the reaction is carried out in an inert atmosphere.

The products of the reactions described herein are isolated by conventional means such as extraction, crystallisation, distillation, chromatography and the like.

Starting materials for the processes described herein are known or can be prepared by known processes from commercially available chemicals.

Detailed Description of the Invention

The invention will now be described in greater detail with reference to the following example, which are given by way of illustration only and are not to be construed as limiting.

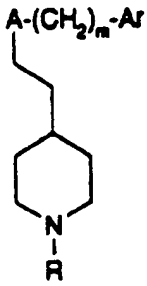
Example 1

4-[2-(3,4-dichlorophenoxy)ethyl]-1-pentylpiperidine, hydrochloride.

Quinuclidine (1.11 g, 10 mmol) was quarternized by heating with 1-bromopentane (1.51 g, 10 mmol) without solvent for one hour at 110°C. To this salt was then added 3,4-dichlorophenol (2.44 g, 15 mmol) and cesium carbonate (3.26 g, 10 mmol). The flask was flushed with nitrogen and the mixture was heated to 170°C (bath temperature) for 15 hours. After cooling to room temperature, the crude product was dissolved in a mixture of ether (50 ml) and water (50 ml). The phases were separated and the aqueous layer was extracted once more with a 50 ml portion of ether. The combined organic phases were dried over magnesium sulphate. Pure 4-[2-(3,4-dichlorophenoxy)ethyl]-1-pentylpiperidine, according to TLC (CH_2Cl_2/EtOH, 9:1), could then be precipitated as the hydrochloride by the addition of methanolic HCl (2.5 mL of a 4.3 M solution). Yield: 3.0 g (7.9 mmol), 79% from quinuclidine. Mp 177-178°C (Lit. 177-178°C), The melting point rose to 178-179°C when the product was recrystallized from a mixture of methanol and ethyl acetate (1:1). The ^{1}H NMR spectrum at 500 MHz and the EI mass spectrum of the product was in accordance with the structure.

CLAIMS:

1. A process for the preparation of substituted 4-ethyl-piperidines having the formula



or a salt thereof

wherein

R is (aryl)$_p$alkyl, (aryl)$_p$alkenyl or (aryl)$_p$alkynyl, wherein the aryl groups may be substituted; cycloalkyl; or cycloalkylalkyl;

p is 0, 1 or 2;

m is 0, 1, 2, 3, 4, 5 or 6;

A is O, S or NR^1, wherein R^1 is hydrogen, alkyl or phenylalkyl; and

Ar is aryl or heteroaryl, each of which may be substituted; which comprises the step of reacting a quinuclidinium salt of formula

wherein R is as defined above and Y is a counter ion, with a compound of the formula HA-(CH$_2$)$_m$-Ar or a reactive derivative thereof, and thereafter optionally forming a salt thereof.

2. A process as in claim 1, wherein A is O.

3. A process as in claim 1, wherein m is 0 and Ar is 3, 4-dichlorophenyl.

4. A process as in claim 1, wherein R is pentyl.

5. A process as in claim 1, wherein the reaction takes place in the presence of a base.

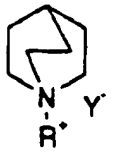
6. A process as in claim 5, wherein the base is an inorganic base.

7. A process as in claim 6, wherein the base is Cs_2CO_3.

8. A compound of the formula

wherein R and Y is as defined in claim 1; provided that when R is alkyl, the alkyl group contains at least three carbon atoms, and Y is not bromide.

9. The use of a compound of the formula



wherein R and Y are as defined in claim 1, as an intermediate in the preparation of the substituted 4-ethyl-piperidines in claim 1.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/EP 95/04975

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/22 C07D453/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEM. LETT. (1987), (6), 1187-90 CODEN: CMLTAG;ISSN: 0366-7022, 1987 IBATA, TOSHIKAZU ET AL 'Nucleophilic substitution of aromatic halides with amines under high pressure' see page 1190 ---	8
Y	WO,A,92 02502 (SMITHKLINE) 20 February 1992 cited in the application see the whole document ---	1-9
A	WO,A,93 15052 (SMITHKLINE BEECHAM) 5 August 1993 cited in the application see the whole document ---	1-9
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 March 1996	15.04.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Kissler, B

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 95/04975

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	ORG. PREP. PROCED. INT. 27(5), 571-2 CODEN: OPPIAK;ISSN: 0030-4948, October 1995 AXELSSON, OSKAR ET AL 'One-pot synthesis of 4-[2-(3,4-dichlorophenoxy)ethyl]-1-pentylpiperidine hydrochloride (SB 201823-A)' see the whole document	1-9
X	MACROMOLECULES (1992), 25(18), 4464-8, LU, CAIXIA; GUNATILLAKE, PATHARIJA; ODIAN, GEORGE 'Zwitterionic polymerization of 1-[(4-carboxyphenyl)methyl]quinuclidin' see formula 1	8
Y	J. CHEM. SOC. D (1970), (5), 297-8 CODEN: CCJDAO, 1970 PIETRA, FRANCESCO ET AL 'Reaction of 2-iodocyclohepta-2,4,6-trien-1-one with 1-azabicyclo[2.2.2]octane. Unusually easy nucleophilic opening of a bicyclo[2.2.2]octane skeleton' see the whole document	1-9
X	CHEM.-ZTG. (1985), 109(10), 333-9 CODEN: CMKZAT;ISSN: 0009-2894, 1985 SCHMIDT, ARTHUR H. ET AL 'Oxocarbons and related compounds. IX. On the three-component reaction squaric dichloride-amine-water: further nitrogen betaines of squaric acid and generation of ammonium salts of squaric monochloride and preparation of squaric amide chlorides' table 2, ex. 9i	8
X	J. ORG. CHEM. (1988), 53(7), 1475-81 CODEN: JOCEAH;ISSN: 0022-3263, 1988 KORNBLUM, NATHAN ET AL 'Electron-transfer substitution reactions: leaving groups' see scheme, structure XIII	8
X	J. ORG. CHEM. (1985), 50(25), 5440-1 CODEN: JOCEAH;ISSN: 0022-3263, 1985 JUNG, MICHAEL E. ET AL 'Alkenyltrialkylammonium salts as dienophiles in Diels-Alder reactions: preparation, cycloadditions, and further reactions..beta.-(Dimethylamino)acrylonitrile equivalent in cycloadditions' see table 1, row three	8

-/--

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/EP 95/04975

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ACTA PHARM. SUEC. (1984), 21(5), 271-94 CODEN: APSXAS;ISSN: 0001-6675, 1984 LINDBORG, BJOERN ET AL 'Troxonium-like inhibitors of the high affinity uptake of choline in mouse brain synaptosomes in vitro' scheme 3, formula 114	8
X	STUD. SURF. SCI. CATAL. (1994), 84(ZEOLITES AND RELATED MICROPOROUS, PT. A.), 29-36, HARRIS, T. V.; ZONES, S. I. 'A study of guest/host energetics for the synthesis of cage structures' table I, formula VII	8
X	LANGMUIR (1991), 7(6), 1107-11, BACALOGLU, RADU; BLASKO, ANDREI; BUNTON, CLIFFORD A.; CERICHELLI, 'Segmental motions of free and micellized cationic surfactants.' Cetyl quinuclidine chloride	8
X	PATENT ABSTRACTS OF JAPAN vol. 14 no. 359 (E-959) [4302] ,3 August 1990 & JP,A,02 125410 (NIPPON CHEMI-CON CORP.) 14 May 1990, n-Propylquinuclidine	8
X	CHEM. BER. (1990), 123(8), 1687-90, SUNDERMEYER, WOLFGANG; WALDI, JOACHIM 'Synthesis and reactions of quinuclidine stabilized sulfenes,' see page 1688	8
A	BULL. CHEM. SOC. JPN. (1987), 60(10), 3499-504, INAMURA, KENGO; NOGAMI, TAKASHI; SHIROTA, YASUHIKO 'The phase transitions of 1-alkyl-1-azoniabicyclo[2.2.2]octane' see figure 1	8
A	ARCH. PHARM., vol. 317, - 1984 WEINHEIM, pages 1010-1017, K. A. GUPTA ET. AL. 'Syntheses and Biological Activities of 1,4-Disubstituted Piperidines' see the whole document	1

-/--

INTERNATIONAL SEARCH REPORT

Interna. Application No
PCT/EP 95/04975

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. MED CHEM., vol. 27, no. 7, 1984 pages 875-881, J. BAGLI ET. AL. 'Troponoids' scheme IV, ex. 24	1-9

INTERNATIONAL SEARCH REPORT

Int. ional application No.
PCT/EP 95/04975

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 8 has been searched incompletely ./.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

The definition of the following substituent(s) is too general and/or encompasses too broad a range of totally different chemical groups, only partly supported by examples given in the descriptive part of the application:

R, p (claim 8)

The search revealed too many relevant documents and/or compounds so that the search report shall not be considered complete.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP 95/04975

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9202502	20-02-92	AP-A-	279	01-08-93
		AU-B-	8327191	02-03-92
		CN-A-	1061963	17-06-92
		EP-A-	0542846	26-05-93
		JP-T-	6500093	06-01-94
		NZ-A-	239268	27-06-94
WO-A-9315052	05-08-93	AU-B-	3364493	01-09-93
		EP-A-	0629190	21-12-94
		JP-T-	7503461	13-04-95